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Local sleep spindle modulations in relation to specific memory cues

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ABSTRACT

Sleep spindles have been connected to memory processes in various ways. In addition, spindles appear to be modulated at the local cortical network level. We investigated whether cueing specific memories during sleep leads to localized spindle modulations in humans. During learning of word–location associations, words presented in the left and right visual hemifields were paired with different odors. By presenting a single odor during a subsequent nap, we aimed to selectively reactivate a subset of the studied material in sleeping subjects. During sleep, we observed topographically restricted spindle responses to memory cues, suggesting successful reactivation of specific memory traces. In particular, we found higher amplitude and greater incidence of fast spindles over posterior brain areas involved in visuospatial processing, contralateral to the visual field being cued. These results suggest that sleep spindles in different cortical areas reflect the reprocessing of specific memory traces.

Introduction

Memories appear to be reprocessed during sleep, leading to consolidation and reorganization of previously acquired information (Cox et al., 2014; Takashima et al., 2009; Talamini et al., 2008). In recent years, sleep spindles have attracted considerable attention as potential neurophysiological markers of such reprocessing (Fogel and Smith, 2011; Lüthi, 2013). Short bouts of cortical oscillatory activity generated by the thalamus, sleep spindles occur in the electroencephalogram (EEG) during both light sleep and slow wave sleep (SWS). Due to their thalamic dependence, spindles have classically been viewed as suppressing the flow of incoming sensory information, a view that is supported by recent evidence (Dang-Vu et al., 2011). Furthermore, spindles may be classified as either slow (10–13 Hz) or fast (13–16 Hz). Slow and fast spindles have different EEG scalp topographies (Zeitlhofer et al., 1997), and are co-active with hemodynamic responses in different cortical regions (Schabus et al., 2007).

Notwithstanding a potential gatekeeping role for spindles, recent evidence has strongly implicated spindle rhythms in the reprocessing of previously encoded information. Besides having plasticity-inducing capabilities in vitro (Rosanova and Ulrich, 2005), sleep spindles are affected by prior learning (Gais et al., 2002) and have been associated with systems-level memory consolidation processes (Buzsáki, 1996; Diekelmann and Born, 2010), as evidenced by their correlation with memory retention across sleep (Cox et al., 2012; Griessenberger et al., 2013; Nishida and Walker, 2007; Schabus et al., 2004). Moreover, pharmacologically induced increases in spindle occurrence lead to improved memory, providing even stronger support for a mechanistic role of spindles in memory consolidation (Mednick et al., 2013). Of special relevance are findings suggesting that the scalp topography of memory-related spindle involvement reflects the nature of the pertaining memory traces. In particular, retention of verbal material is related to spindles recorded over frontal brain regions (Clemens et al., 2005), while parietal spindles correlate with spatial memory (Clemens et al., 2006). In the procedural realm, unilateral motor memory consolidation depends on the balance between spindle occurrence over contra- and ipsilateral premotor cortices (Nishida and Walker, 2007). Combined with evidence demonstrating that spindles may be locally regulated (Nir et al., 2011), these distinct topographies raise the possibility that spindles constitute instances of memory trace reactivation that are tied to the regional cortical networks harboring the specific memories being reprocessed. This suggestion is based, however, on separate studies employing different study materials. Moreover, given the low surface electrode coverage in the pertaining studies, the allocation of recorded signals to specific cortical areas remains speculative.

To test the hypothesis of local memory-related spindling directly, we adopted an approach in which subjects were required to learn word–location associations. The associations were presented in blocks that were spatially biased to either the left or the right visual field. Each associational category (i.e., each block) was paired, during learning, with an odor that served as a reactivation cue during subsequent sleep. During sleep, we recorded high-density EEG for post-hoc sleep spindle analysis. We used odors for cueing because they have been

Abbreviations: EEG, electroencephalography; SWS, slow wave sleep; REM, rapid eye movement; NREM, non-rapid eye movement; CSD, current source density; fMRI, functional magnetic resonance imaging.

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applied successfully in the past (Diekelmann et al., 2011; Rasch et al., 2007), because odor cue effects are very specific (Rihm et al., 2014), and because odors carry a limited risk of waking the participant relative to auditory stimulation (Carskadon and Herz, 2004).

With this setup we aimed to assess whether the two cueing conditions induce differential topographies of spindle modulations. This would support the notion that spindles respond in a local and memory-specific manner to reactivation cues. More specifically, we expected responses over parieto-occipital brain areas contralateral to the hemifield bias of the cued word block. We predicted involvement of these regions because they are known to process visuospatial aspects of stimuli (Kravitz et al., 2011). Importantly, these areas show contralateral activity to unilaterally encoded (Kuo et al., 2012; Vogel and Machizawa, 2004) or attended visual information (Capilla et al., 2014; Händel et al., 2011), as well as during retrieval of spatially lateralized stimuli in working memory (Medendorp et al., 2005; Sereno et al., 2001; Van Der Werf et al., 2013) and long-term memory tasks (Takashima et al., 2007). Thus, lateralized parieto-occipital spindle responses to hemifield-related odor cues would support the hypothesis that spindles reflect the nature of reactivated representations.

Methods

Participants

This study was approved by the local ethics committee of the University of Amsterdam and all subjects provided written informed consent. Twenty-eight right-handed subjects (25 female, age: 20.1 [mean] ± 2.3 [SD], range: 18–29 years) who reported no history of psychiatric or neurological disorders participated in the study. All were good habitual sleepers and were asked to wake up no later than 8.30 AM on the day of participation. Furthermore, they reported not taking any psychoactive substances in the 24 h before the experiment, or more than one caffeine-containing beverage in the 6 h before participation. Participants were rewarded with either course credits or monetary compensation.

Procedure overview

Fig. 1A shows an overview of the experimental procedure. Subjects reported to the sleep laboratory at noon and filled out questionnaires regarding sleep habits and sleep on the prior night, before being prepared for EEG registration. Next, they performed a practice run of the memory task (see Supplementary methods). Participants were then fitted with a nasal cannula that was connected to an odor dispenser and were asked to perform an odor detection task. This task served to ensure that the odors used as reactivation cues were perceived by all subjects. Next, subjects performed the main memory task with odor stimulation and subsequent retrieval. During the ensuing two-hour sleep opportunity with high-density EEG registration, odor cueing of hemifield-biased associations was carried out in a between-subject fashion. That is, each sleeping subject was cued with only one of the odors presented during encoding. Upon waking, participants were allowed to recover from sleep inertia for about 45 min before starting the delayed memory retrieval session around 6 PM. The interval between the first and second retrieval sessions was kept constant at 3 h. Finally, an exit questionnaire probed issues regarding learning strategy, odor delivery and sleep cueing. Total duration of the experimental session was approximately 6.5 h. All tasks were presented using Presentation software (Neurobehavioral Systems, Albany, CA), while subjects were seated approximately 50 cm away from a 17" screen.

Odor delivery and detection

Four distinct odors were used during the encoding phase of the main task. Two milliliters of each of the single-molecule odorants ionone beta, silvial, tetrahydro linalool and undecavertol (Perfumer's Apprentice, Capitola, CA), was mixed with 1 ml odorless dipropylene glycol. A custom-built odor dispenser located outside the experimentation room forced air through one of five glass jars; four containing diluted odor and an empty one to keep total resistance constant when administering neutral air. Odors were delivered via ~5 m long polytetrafluoroethylene tubing to the nasal cannula worn by the subject. Participants quickly adapted to the constant, light air flow.

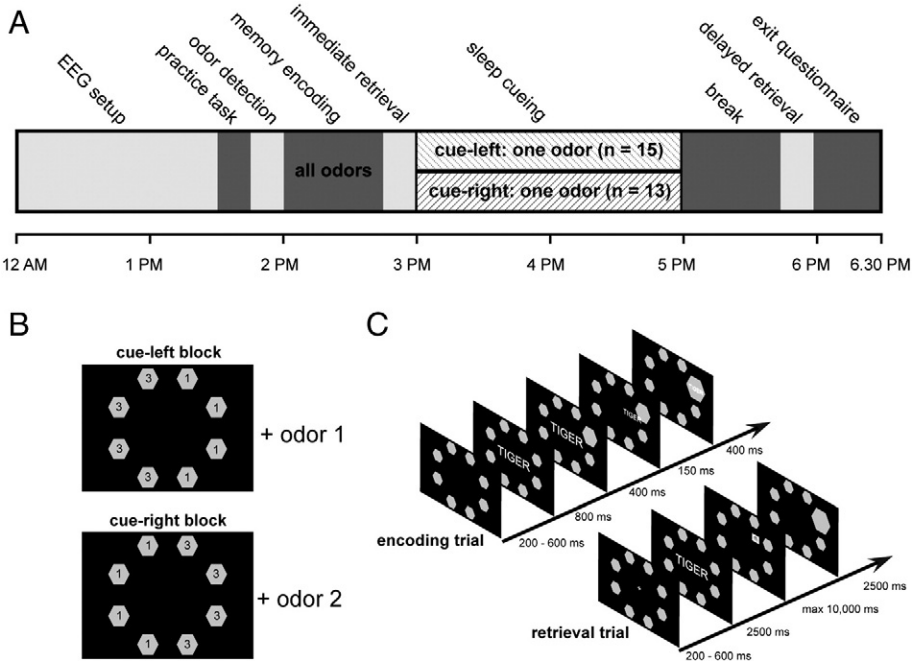

Fig. 1. Experimental procedure. (A) Timeline showing approximate timing of the various parts of the experimental procedure. (B) Schematic representation of word–location assignments for cue-left (top) and cue-right (bottom) word blocks. The numbers in each of the 8 locations indicate how many words were associated with that position. A block consisted of 16 words in total and was consistently paired with one odor. (C) Encoding (top) and retrieval (bottom) trial timing.

The odor dispenser was computer-controlled to switch pairs of valves and restrict the airflow to pass through one jar only, thereby preventing cross-contamination with any of the other odors.

Following the practice task (see Supplementary methods), all four odors were presented in random order twice for 30 s to assess subjective odor intensity and pleasantness. After each odor presentation, subjects were asked to rate intensity and pleasantness for that odor on a 5-point scale. Subsequently, neutral air was presented for 30 s before the next odor was administered. Ratings from the final presentation round were used for analysis.

Memory task

The memory task we used contained a part that was not relevant for the current experiment (i.e., items that were learned, but were not reactivated or otherwise used in the experiment). We here describe the memory task as it relates to the findings presented in this paper. For a complete description of the memory task, see the Supplementary methods. In the encoding phase, subjects were asked to associate each of 32 concrete two-syllable words with one of eight screen locations. The associative items were presented in two blocks (of 16 words each) that were biased to either the left or right visual hemifield. Specifically, the leftward bias was operationalized by pairing the four screen locations on the left side with three words each (totaling twelve left-sided stimuli), and the four screen locations on the right with only one word each. This pattern was reversed for the word block with a rightward bias (Fig. 1B). During encoding, each of these blocks was presented with concurrent administration of one distinct contextual odor. We implemented biases to either side, rather than full-fledged lateralization (i.e., all words from a block to one side), to obscure the relations between word blocks and screen side. With fully lateralized word blocks, subjects might have become aware of these associations, complicating the calculation of chance level performance at retrieval.

Six learning rounds were offered with one-minute breaks in between. This high number of encoding rounds was chosen to allow for the formation of relatively strong memory traces that may be easier to reactivate during subsequent sleep. Importantly, block-odor pairing remained constant throughout the learning session.

Presentation of a word block began with administration of the odor to be associated with the upcoming word block. Subjects were asked to press a button upon perceiving the odor. The word block then started under continuous odor delivery. Each single trial (Fig. 1C, top) started with a screen showing all eight target locations (small-sized gray octagons with green borders) against a black background for an average of 400 ms (jittered between 200 and 600 ms). Then a word was presented in white capital letters in the middle of the screen for 800 ms. Next, the target location enlarged (to medium-sized) for 400 ms, and the word stimulus moved towards the medium-sized target location in 150 ms while font size decreased. Finally, the word remained visible in the now large-sized octagon for another 400 ms before the next trial started. Presentation of a full word block with concurrent odor delivery took approximately 35 s.

Following the last stimulus of the word block the odor device was switched back to neutral air. Now subjects performed a self-paced distractor task (counting back in threes from a three-digit starting number and indicating whether a target number was part of that sequence), pressed a button to confirm that they did not smell the odorant anymore, performed another trial of the distractor task, and continued into the next word block. The distractor tasks (total duration 20 to 40 s) minimized subjects' opportunity to rehearse material and devise learning strategies.

Word-to-block assignment and word-to-location assignment were randomized for each subject with the proviso that the same location could not occur twice in a row. This was done to limit the formation of links between words occurring at the same location. Block order within each learning round was also randomized. Furthermore, block-to-odor assignment was counterbalanced across subjects.

Both immediately following memory encoding, and after three hours containing a nap, memory was tested. To this purpose all learned words were shown sequentially in random order. Subjects were required to move a cursor to the correct locations with a joystick using their right hand. No odors were present during testing. Each retrieval trial (Fig. 1C, bottom) started with a white fixation cross in the middle of the screen and the eight target locations for 400 ms (jittered between 200 and 600 ms), followed by central word presentation for 2500 ms. Thereafter, the word was replaced with a cursor in the center of the screen. Subjects had 10 s to select one of the eight locations. When the cursor was near a selectable location, that octagon became medium-sized. After selection of a location by means of a button press on the joystick, the octagon turned large-sized and remained that way for 2500 ms until the next trial started. No feedback was provided regarding accuracy. Total duration of the retrieval task was about 10 min.

Sleep cueing

Subjects went to bed in a quiet, dark room wearing the EEG setup and nasal cannula. At this time, the odor dispenser was continuously delivering neutral air. Polysomnographic signals were monitored online to track sleep progress. Upon visual identification of non-rapid eye movement (NREM) sleep (i.e., stages 2, 3 or 4), the cueing protocol was initiated. During cueing, a single odor, corresponding to a cue-left or cue-right word block, was presented automatically in a 30 s on-off fashion to counter habituation processes (Rasch et al., 2007). Fifteen subjects underwent cueing of the leftward biased word block (cue-left condition); thirteen received the cue for the rightward biased block (cue-right condition). As soon as subjects showed signs of movement, rapid eye movement (REM) sleep or waking up, the cueing was paused (i.e., neutral air was presented continuously again). If NREM sleep returned, cueing was resumed. Thus, we attempted to selectively reactivate word stimuli that were predominantly associated with either the left or right visual field.

EEG acquisition, sleep and spindle analysis

EEG was acquired using a 128-channel WaveGuard cap (ANT, Enschede, The Netherlands) with electrode placement according to the 10–5 system (Oostenveld and Praamstra, 2001). Horizontal and vertical electrooculography and chin electromyography were monitored with bipolar derivations. Signals were sampled at 512 Hz using either one 136-channel, or two cascaded 72-channel Refa DC amplifiers with a low-pass filter at one fifth of the sample rate (TMS International, Enschede, The Netherlands). EEG was referenced to Cz and impedance levels were kept below 10 kΩ.

Sleep stages were scored offline using Galaxy software (PHIi, Amsterdam, The Netherlands) with an epoch size of 30 s in accordance with standard criteria (Rechtschaffen and Kales, 1968). Sleep scoring was performed blind to cueing condition (cue-left/cue-right) and odor onset/offset times. Sleep parameters, including sleep latency, total sleep time and time spent in different sleep stages, were calculated.

Custom Matlab scripts were combined with several freely available toolboxes for all subsequent analyses. Functions from the EEGLAB toolbox (http://sccn.ucsd.edu/eeglab) were used to high-pass (0.1 Hz) and notch filter (50 Hz) the raw EEG data, interpolate channels displaying artifacts during periods of sleep, and re-reference the EEG to linked mastoids. Next, current source density (CSD) was estimated with a spherical spline algorithm (Perrin et al., 1989), as implemented in the CSD toolbox (http://psychophysiology.cpmc.columbia.edu/software/csdtoolbox/index.html). The CSD approach minimizes the effects of volume conduction by calculating the second spatial derivative of the scalp potential, estimating local radial current flow. We

adopted this approach to maximize opportunities to detect local spindle responses.

Sleep spindles were identified in sleep stages 2, 3 and 4, using an automated dynamic thresholding procedure similar to one described previously (Ferrarelli et al., 2007). For each subject and each channel separately, the signal was zero-phase band-passed between 10 and 16 Hz with a 4th order IIR filter, rectified, and its envelope was calculated. Whenever the envelope exceeded an upper threshold a potential spindle was detected. Crossings of a lower threshold before and after this point marked the beginning and end, respectively, of the spindle. Per channel, thresholds were set at the average envelope amplitude in stage 2 sleep + 3 SD (upper threshold), and + 0.5 SD (lower threshold). We took the novel approach of basing the spindle thresholds on stage 2 sleep (instead of on all spindle-containing NREM sleep), because on some electrodes we observed a smaller envelope amplitude in SWS compared with stage 2 sleep (C4: $t(25) = 5.2$, $P < 0.0001$; C3: $t(25) = 1.6$, $P = 0.13$). Thus, threshold setting based on combining light and deep sleep would be confounded by the relative contribution of both. Since some of our subjects showed very little SWS, while all showed sufficient amounts of light sleep, we used stage 2 sleep to calculate spindle thresholds that were unrelated to the amount of deep sleep. While this approach might bias spindle detection towards light sleep somewhat, spindle density values suggest that this was not the case (see Table 2 and Inline Supplementary Fig. S1). Identified spindles with a duration of <500 ms or >3000 ms were discarded.

To further decrease the probability of detecting spurious spindles, we applied two sequential steps. First, a Fast-Fourier transform was applied to the raw (CSD-transformed) EEG of each detected spindle event. A genuine spindle would be expected to display a spectral peak in the sigma (10–16 Hz) range but not in higher frequency bands. Whenever the natural logarithm of the normalized power of any frequency bin between 20 and 80 Hz exceeded that of any frequency in the spindle range, the detected event was deemed to reflect an artifact. Second, spindles with an average amplitude exceeding 4 SD were considered to be outliers and removed.

Depending on their center frequency, remaining spindles were classified as slow (<13 Hz) or fast (>13 Hz). Additionally, spindles were classified as occurring during cue-on or cue-off periods. For this, we extracted cue-on data segments of 25 s duration starting from 5 s after odor onset until neutral air onset, and the corresponding number of adjacent cue-off data segments (also of 25 s duration). The first 5 s of each segment were removed to avoid contamination with the previous cue-on/cue-off period. Spindles having their maximum amplitude in cue-on or cue-off data segments were labeled as such. For each combination of slow/fast and cue-on/cue-off spindles, spindle measures were determined. Average spindle envelope amplitude and spindle density (counts per minute) were calculated across all NREM sleep (stages 2, 3, and 4). Finally, when a measure could not be computed, for example when no spindles of a certain type were detected in a given channel, we interpolated these measures from surrounding electrodes. This was done to avoid varying numbers of observations for different electrodes, which would complicate statistical procedures.

Because of the existence of large inter-individual and inter-electrode variability in spindle characteristics, we wished to adjust for these differences. Furthermore, we reasoned that effects of cueing side on spindle measures should be tied to the actual presence of the odor. This allowed us to apply a normalization approach in which we directed our attention to cue-on epochs and adjusted cue-on spindle values for the corresponding cue-off values. We did this separately for each electrode, by regressing cue-on spindle values onto cue-off values across all subjects. Resultant residuals reflect baseline-corrected spindle responses, where values >0 indicate a response greater than expected based on cue-off spindles, and values <0 indicate a response smaller than expected. It is these locally adjusted spindle measures that we subsequently used for analysis. For statistical analysis, we performed permutation-based statistics with cluster correction using the Fieldtrip toolbox (http://fieldtrip.fcdonders.nl/). We compared cue-left and cue-right groups across 1000 iterations, using the independent samples t statistic, a clusteralpha value of 0.15, and a significance threshold of 0.05, resulting in significant clusters at $P < 0.025$ for two-sided testing.

Results

Odor assessment

Odor intensity ratings did not significantly differ among the four odors (Friedman test: $\chi^2(3) = 6.6$, $P = 0.09$), but odor pleasantness was found to differ (Friedman test: $\chi^2(3) = 10.4$, $P = 0.016$). Follow-up Wilcoxon Signed Rank tests revealed that odor three was rated more positively than all other odors (all $Z < -2.3$, all $P < 0.03$, uncorrected). However, all four odors were used as sleep cues approximately equally often (Inline Supplementary Table S1), and to the same extent in cue-left and cue-right groups (χ^2 test of independence: $\chi^2(3) = 0.4$, $P > 0.9$). Accordingly, average intensity and pleasantness ratings for the odors employed for sleep-cueing did not differ between cue-left and cue-right groups (Mann–Whitney U test, intensity: $Z = -1.1$, $P = 0.26$; pleasantness: $Z = -0.9$, $P = 0.37$). It is therefore unlikely that the specifics of any particular odor influenced our pattern of results.

Inline Supplementary Table S1 can be found online at http://dx.doi.org/10.1016/j.neuroimage.2014.05.028.

Odor cueing and sleep

Cueing took place for an average of 52.1 ± 18.1 min, 48.3 ± 16.0 of which during spindle-containing NREM sleep. These amounts did not differ significantly between the cue-left and cue-right groups (Independent T tests; total cueing time left: 47.3 ± 17.0, total cueing time right: 57.6 ± 18.4, $t(26) = -1.5$, $P = 0.14$; NREM cueing time left: 44.8 ± 15.8, NREM cueing time right: 52.3 ± 15.9, $t(26) = -1.2$, $P = 0.22$). Overall, cueing occurred more during SWS than during stage

Table 1
Sleep architecture parameters (mean ± SD) for the cue-left and cue-right groups.

	Cue-left	Cue-right	t value	df	P
Sleep efficiency (%)	79.7 ± 14.3	82.2 ± 13.8	−0.46	26	0.65
Sleep latency (min)	8.4 ± 6.8	8.8 ± 5.9	−0.18	26	0.86
Total sleep (min)	97.3 ± 17.7	99.0 ± 16.8	−0.26	26	0.80
Wake after sleep onset (min)	12.4 ± 13.0	9.4 ± 13.5	0.60	26	0.55
S1 (min)	21.1 ± 9.1	20.2 ± 13.6	0.21	26	0.84
S2 (min)	38.7 ± 14.2	42.2 ± 16.2	−0.61	26	0.55
S3 (min)	6.4 ± 4.2	9.5 ± 6.9	−1.45	26	0.16
S4 (min)	23.6 ± 11.1	21.5 ± 14.4	0.43	25	0.67
REM (min)	14.9 ± 12.1	11.9 ± 8.0	0.54	13	0.60
SWS (S3 + S4; min)	28.5 ± 13.7	31.0 ± 14.8	−0.47	26	0.64
NREM (S2 + S3 + S4; min)	67.2 ± 17.8	73.3 ± 20.9	−0.83	26	0.41

2 sleep (28.8 ± 13.2 vs. 19.5 ± 13.2 min, Paired T test: $t(27) = -2.3$, $P = 0.028$; see Supplementary material for a discussion of this finding.) Visual inspection of the EEG did not show observable arousal reactions to odor onset or offset. Sleep architecture parameters (Table 1) did not differ appreciably between the cue-left and cue-right groups (Paired T test, all $P > 0.16$). Finally, the exit questionnaire confirmed that none of the participants were able to indicate which odor had been used for sleep cueing.

Memory performance

Memory performance was assessed immediately after learning and 3 h later, following the intervening nap with memory cueing. In order to maximize chances of finding learning-related spindle modulations during sleep, subjects were trained extensively (approximately 1 h) and to high performance levels (87 ± 14% correct). Subjects did not forget significantly across the retention interval, nor did they perform better on cued than on uncued items (2 × 2 within ANOVA: all $F(1,27) < 0.6$, all $P > 0.4$, Fig. 2A). Similarly, there were no significant main or interaction effects of time and cueing on response time (all $F(1,27) < 1.2$, all $P > 0.25$, Fig. 2B).

Given the minimal variance in memory performance, significant correlations between, on the one hand, memory retention, and, on the other hand, cueing and sleep variables could not be expected. Nonetheless, we computed a reactivation advantage measure [(cued delayed score / cued immediate score) / (uncued delayed score / uncued immediate score)], that is potentially sensitive to relative performance shifts from uncued to cued items. However, we did not find reliable relationships correlating this measure with cueing duration or sleep architectural parameters (all $P > 0.4$).

Finally, the exit questionnaire revealed that none of the participants were aware of the relation between odor and visual field at learning. Taken together, these findings indicate that memory performance was not noticeably affected by cueing side, cueing duration or sleep architecture.

Sleep spindles

The automated spindle detection procedure we used contains novel elements (see Methods subsection EEG acquisition, sleep and spindle analysis). It is therefore of interest that general spindle characteristics (Table 2), as well as the scalp distributions of slow and fast spindles (Inline Supplementary Fig. S1) are similar to those reported previously, attesting to the validity of our spindle detection approach.

Inline Supplementary Fig. S1 can be found online at http://dx.doi.org/10.1016/j.neuroimage.2014.05.028.

We compared baseline-corrected (see Methods section) spindle values between the cue-left and cue-right groups. Results of this analysis across all NREM sleep indicated significantly larger amplitudes of fast spindles for the cue-left subjects than for the cue-right group over a right-lateralized parieto-occipital cluster (Fig. 3A, $P < 0.001$). The opposite contrast (cue-right > cue-left) revealed a significant left-lateralized cluster, also with a posterior parietal topography; (Fig. 3B, $P < 0.001$). Fast spindle density was similarly affected by the memory cue: the cue-right group showed a significantly higher rate of spindles in a left parieto-occipital area than the cue-left group (Fig. 3C, $P < 0.001$). The opposite contrast, however, did not reveal reliable differences. Considering slow spindles, we observed a right-lateralized temporal cluster where spindle amplitude was larger for the cue-right than for the cue-left group (Supplementary Fig. 2A, $P < 0.001$), and a left-lateralized parieto-occipital cluster of higher spindle density in the cue-left as compared to the cue-right condition (Supplementary Fig. 2B, $P < 0.001$). However, slow spindle clusters were comprised wholly of electrodes at the outer rim of the array, warranting caution when interpreting these effects. Regardless, combined, these findings support the notion that spindles respond in a local and memory-specific manner to reactivation cues.

In line with our prediction, the pattern of fast spindle modulations induced by each cue encompassed parieto-occipital areas contralateral to the hemifield bias of the cued memories. To explore the possibility of spatially symmetrical, contralateral spindle modulations in these areas, we performed additional analyses. We selected the three posterior clusters showing a significant cueing effect for fast spindles in the previous analysis, along with their contralateral counterparts (6 clusters with 16 electrodes in total), and averaged the values within each cluster. For each cluster-pair, a 2 × 2 mixed ANOVA was performed with factors hemisphere and cueing side. Interestingly, all clusters showed a significant crossover interaction between hemisphere and cueing side, but no main effects (small cluster spindle amplitude interaction: $F(1,26) = 5.4$, $P = 0.029$, partial $\eta^2 = 0.17$; big cluster spindle amplitude interaction: $F(1,26) = 9.5$, $P = 0.005$, partial $\eta^2 = 0.27$; cluster spindle density interaction: $F(1,26) = 7.3$, $P = 0.012$, partial $\eta^2 = 0.22$; all main effects: $P > 0.2$). Specifically, for both spindle amplitude and spindle density, cueing had opposite effects on contralateral and ipsilateral posterior brain regions, such that the cued hemisphere showed a relative increase of spindling while the uncued hemisphere displayed a relative decrease

Table 2
Spindle characteristics (mean ± SD) for channel FCz during NREM (S2 + S3 + S4) sleep.

Slow spindles	Density	3.1 ± 1.4
	Amplitude	213 ± 71
Fast spindles	Density	2.2 ± 0.9
	Amplitude	217 ± 70
All spindles	Density	5.2 ± 1.5
	Amplitude	215 ± 70

Note: Spindle density in counts per minute, spindle amplitude in nV/cm^2. N = 27 due to noisy signal for one subject.

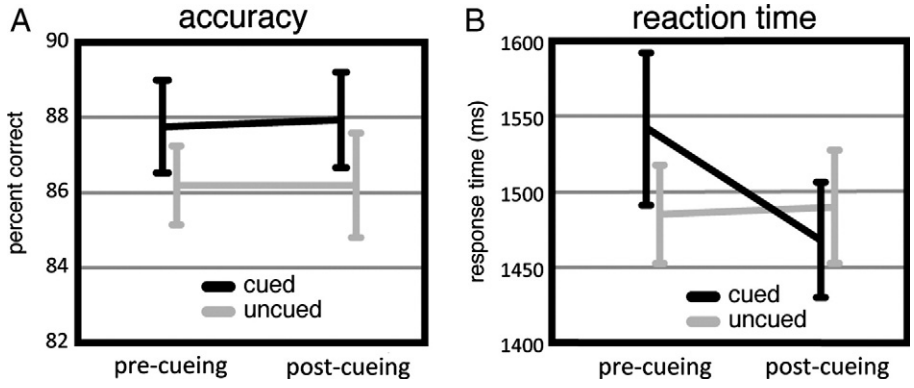

Fig. 2. Memory performance (mean ± SEM) pre- and post-nap cueing. (A) Memory accuracy for cued and uncued items. (B) Response times for cued and uncued items.

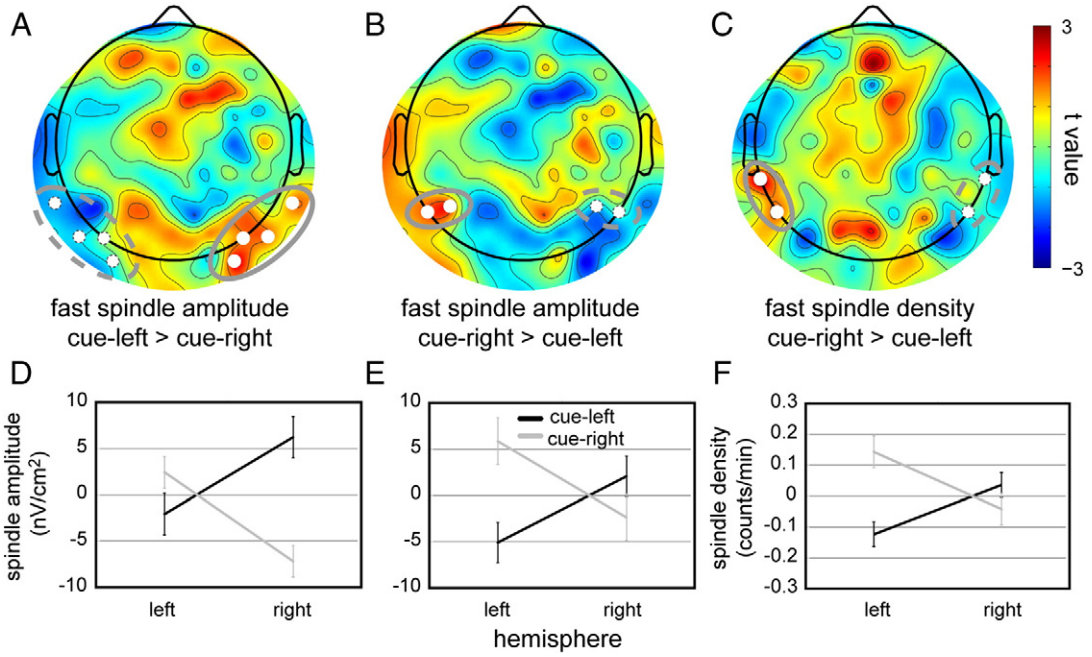

Fig. 3. Fast spindle effects. (A–C) T maps showing significant cueing side effects. Gray solid ovals mark significant clusters; significant electrodes in each cluster are shown as white dots. Gray dashed ovals depict contralateral 'mirror' clusters used for assessing hemisphere-dependence of cueing side effects in (D–F). (A) A right parieto-occipital region (electrodes PO8, TPP10h, PPO10h, and POO10h) responded with higher spindle amplitude in the cue-left than in the cue-right condition. (B) A left parietal site (P5, P7) showed increased spindle amplitude in the cue-right relative to the cue-left group. (C) Enhanced spindle density in a left parietal region (P7, TP7) in the cue-right group, as compared to the cue-left group. (D–F) Significant crossover interactions between cueing side and hemisphere for all clusters indicate bilaterally symmetrical spindle modulations in response to memory cues.

(Figs. 3D,E,F). Follow-up one-sample T tests comparing the baseline-corrected spindle values to zero, performed separately for each of the six clusters, and separately for the cue-left and cue-right groups, revealed fairly reliable up- or down-regulated spindle activity in a number of instances (cue-left group, left spindle density cluster: $t(14) = -1.8$, $P = 0.086$; cue-right group, left spindle density cluster: $t(12) = 2.1$, $P = 0.054$; cue-right group, right spindle amplitude big cluster: $t(12) = -2.4$, $P = 0.03$). Yet, these effects did not survive the Bonferroni adjustment for multiple tests (twelve comparisons in total). However, in light of the relatively low number of observations in these comparisons (fifteen and thirteen for cue-left and cue-right, respectively), statistical power to detect differences was relatively low. In sum, we found symmetrical spindle responses specifically for parieto-occipital regions, such that odor cueing increased contralateral fast spindle amplitude and density while reducing the ipsilateral response.

Finally, we assessed whether spindle amplitudes and densities in the abovementioned areas were correlated with memory performance, but we did not observe any reliable associations.

Discussion

In this experiment, odor-cued reactivation of spatially specific subsets of memories led to fast spindle amplitude and density modulations with differential topographies. Moreover, odor-specific modulations of fast spindles were restricted to parieto-occipital regions of the dorsal stream of visual processing. These posterior regions displayed a striking lateralized response pattern, which is consistent with their involvement in egocentric spatial processing and their tendency to respond preferentially to information presented in the contralateral visual field (Kravitz et al., 2011). Thus, sleep spindles react locally in relation to specific memories, with a scalp topography consistent with the underlying nature of those memories.

Our main finding of differentially localized spindle responses for different reactivation cues ties in with accumulating evidence that sleep is not a unitary, brain-wide phenomenon. Local circuits may show more or less sleep pressure depending on prior wake involvement in information processing (Huber et al., 2004, 2007), and sleep may be expressed locally in an otherwise waking brain (Vyazovskiy et al., 2011). Similarly, slow oscillations and sleep spindles can be restricted to local networks (Massimini et al., 2004; Nir et al., 2011). Importantly, while previous studies have linked local spindles to memory (Clemens et al., 2005, 2006; Nishida and Walker, 2007), these interpretations were not unequivocal as they relied on few recording sites and distinct memory material. In the present study, however, all participants encoded precisely the same material before undergoing differential sleep cueing. This enables us to attribute spindle effects unambiguously to the cueing protocol, without there being any confounds from potential encoding differences. Thus, our findings demonstrate that regional spindle responses can be specific for a particular type of memory, which suggests that these responses reflect the nature of the memory material that is being reprocessed.

This interpretation is further supported by the fact that regional fast spindle responses were restricted to parieto-occipital areas known to be relevant for spatial processing (Kravitz et al., 2011). For spindle amplitude, both cueing conditions (cue-left and cue-right) revealed responses significantly lateralized to the parieto-occipital region contralateral to the cued visual hemifield. While spindle density only displayed this contralateral parietal effect for the cue-right > cue-left contrast, additional analyses demonstrated that cueing-side effects depended reliably on the hemisphere, for both spindle density and spindle amplitude. Given this response profile, it is tempting to speculate that we uncovered cue-related reactivation of visuospatial memory traces, as the same profile characterizes involvement of parieto-occipital areas during the encoding, maintenance and retrieval of spatially lateralized stimuli (Kuo et al., 2012; Medendorp et al., 2005; Sereno et al., 2001; Takashima et al., 2007; Van Der Werf et al., 2013; Vogel and Machizawa, 2004). Taking into consideration that the primary aspect that differed between the cueing conditions was the spatial location of the items being cued, this account seems most plausible.

Considering these lateralized parieto-occipital responses more closely, we established that spindle effects were simultaneously positive for brain areas contralateral to the cued hemifield, and negative for homologous ipsilateral scalp regions. Interestingly, bilaterally opposite fMRI responses similar to ours have been demonstrated in the thalamus in response to a visuospatial attention task (Cotton and Smith, 2007). Additionally, posterior alpha power is enhanced ipsilateral to the attended visual hemifield, which is thought to inhibit processing of unattended stimuli (e.g., Capilla et al., 2014; Händel et al., 2011). Thus, from a functional perspective, opposite spindle modulations in the two hemispheres may reflect a more general feature of visuospatial processing whereby activity in the less pertinent hemisphere is suppressed, perhaps to reduce interference or to accommodate capacity limits.

The modulations we report are expressed as effects on both fast spindle amplitude and spindle density. In general, signal amplitudes reflect the extent of synchrony and excitability of the underlying neural population (Buzsáki et al., 2012). Thus, spindle amplitude could indicate local cortical responsiveness. Supporting this view, a recent combined EEG–fMRI study showed that, during sleep, spindle amplitude was correlated with reactivation of cortical areas that had been active during prior memory encoding (Bergmann et al., 2012). Of note, that study also observed a correspondence between spindle amplitude and hippocampal activation. Viewed in this light, we suggest that the amplitude modulations observed in the current study reflect biases of cortical excitability towards the networks associated with the presented memory cues, at the expense of uncued networks. Similarly, spindle density may constitute a measure of the rate at which networks become particularly excitable and plastic. This suggestion of spindle density as a proxy for plasticity is further supported, albeit indirectly, by correlations between spindle density and memory retention from pre- to post-sleep (Cox et al., 2012).

What could be the mechanism underlying these findings? During sleep, odors can activate the hippocampus (Rasch et al., 2007), where the previously acquired links with word–location pairs are presumably stored. Here, odor cue information could bias pattern reactivation towards cue-related neuronal ensembles, as has been described for auditory cues in rats (Bendor and Wilson, 2012). Previous studies suggest that such neuronal replay, which occurs during hippocampal sharp wave–ripple complexes, can recruit associated cortical traces (Ji and Wilson, 2006; Peyrache et al., 2009). This process appears to be gated by spindles, as suggested by the phase locking of hippocampal ripples to spindle oscillations (Clemens et al., 2011) and the aforementioned relation between the hippocampal hemodynamic response and spindle amplitude (Bergmann et al., 2012). Although spindles find their origin in the reticular nucleus of the thalamus (Steriade et al., 1987), neocortical input has been shown to affect spindle characteristics (Bonjean et al., 2011). Thus, reactivated pools of local corticothalamic cells could synchronize thalamic spindle output, thereby modulating EEG-recorded spindle amplitude and rate of spindle occurrence. At present, however, this mechanistic account of our findings is necessarily fragmentary and various aspects thereof need to be further investigated.

In addition to effects on fast spindle characteristics, we observed cue-related effects on slow spindle amplitude and density. In principle, these additional clusters support the idea of topographically restricted memory reprocessing. However, the pertaining clusters consist entirely of edge electrodes, for which Laplacian estimates of local radial current are less reliable (and for which there tends to be more EMG-related noise, even during sleep). Thus, findings of slow spindles should be considered cautiously and will here not be further interpreted.

Still, it is of interest that fast spindles displayed a striking contralateral response pattern, while slow spindles did not. The existence of two types of spindles has garnered increasing support over the years, with slower spindles occurring predominantly frontally, and faster spindles having a centro-parietal topography (Zeitlhofer et al., 1997). We observed very similar topographies in our own data (Inline Supplementary Fig. S1). Of note, fast spindles are more tightly coupled to depolarized slow oscillation up-states than slow spindles (Mölle et al., 2011), and hippocampal ripples are preferentially phase-locked to fast spindle troughs (Clemens et al., 2011). Considering the established importance of both slow oscillations and ripples in memory consolidation, fast spindles are the more likely candidate to be involved in memory processing. Indeed, the few studies explicitly reporting on both spindle types' involvement in offline memory processing all point towards the specific relevance of fast spindles (Barakat et al., 2011; Saletin et al., 2011; Tamaki et al., 2008, 2009; Van der Helm et al., 2011).

Finally, some considerations regarding the current study warrant attention. In particular, design choices were aimed at maximizing the probability of finding cue-related brain responses. Hence, the memory task we employed required intensive encoding over the span of an hour, leading to ceiling performance in some subjects. Consequent to the aforementioned choices, there was no forgetting over the short retention interval afforded by our nap-design and, thus, little opportunity for the emergence of consolidation differences between cued and uncued items. Indeed, cueing was not reflected in memory performance. Previous studies administering external memory cues to sleeping subjects did report memory benefits for cued items in episodic (Diekelmann et al., 2011, 2012; Rasch et al., 2007; Rihm et al., 2014; Rudoy et al., 2009) and procedural tasks (Antony et al., 2012; Schönauer et al., 2013), although there is also evidence of cue-related functional connectivity changes in the absence of an overall memory effect (Van Dongen et al., 2012). Nonetheless, in all these studies there were significant performance changes across the retention interval, allowing for differential effects of reactivated and uncued items. Considering that our experimental design offered little opportunity to uncover effects of reactivation on memory performance, the lack of behavioral effects should not be taken to contradict existing literature.

In conclusion: By marking subsets of memories with distinct contextual odors, we were able to complement and extend the notion of local sleep in demonstrating that sleep spindles react locally in relation to specific memories. These findings suggest that sleep spindles in different cortical areas reflect the reprocessing of specific memory traces.

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